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Abstract: Objective: Huntington's disease (HD) is characterized by psychiatric, cognitive, and motor disturbances. The study aimed to determine electroencephalography (EEG) global state and microstate changes in HD and their relationship with cognitive and behavioral impairments. Methods: EEGs from 20 unmedicated HD patients and 20 controls were compared using global state properties (connectivity and dimensionality) and microstate properties (EEG microstate analysis). For four microstate classes (A, B, C, D), three parameters were computed: duration, occurrence, coverage. Global- and microstate properties were compared between groups and correlated with cognitive test scores for patients. Results: Global state analysis showed reduced connectivity in HD and an increasing dimensionality with increasing HD severity. Microstate analysis revealed parameter increases for classes A and B (coverage), decreases for C (occurrence) and D (coverage and occurrence). Disease severity and poorer test performances correlated with parameter increases for class A (coverage and occurrence), decreases for C (coverage and duration) and a dimensionality increase. Conclusions: Global state changes may reflect higher functional dissociation between brain areas and the complex microstate changes possibly the widespread neuronal death and corresponding functional deficits in brain regions associated with HD symptomatology. Significance: Combining global- and microstate analyses can be useful for a better understanding of progressive brain deterioration in HD.

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HIGHLIGHTS

- Global states underlying Huntington's disease (HD): reduced connectivity and severity related dimensionality increase.
- Microstates in HD: classes A & B more prominent, classes C & D less prominent.
- Cognitive test scores related to global- and microstate properties.

ABSTRACT

Objective: Huntington's disease (HD) is characterized by psychiatric, cognitive, and motor disturbances. The study aimed to determine electroencephalography (EEG) global state and microstate changes in HD and their relationship with cognitive and behavioral impairments.
Methods: EEGs from 20 unmedicated HD patients and 20 controls were compared using global state properties (connectivity and dimensionality) and microstate properties (EEG microstate analysis). For four microstate classes (A, B, C, D), three parameters were computed: duration, occurrence, coverage. Global- and microstate properties were compared between groups and correlated with cognitive test scores for patients.
Results: Global state analysis showed reduced connectivity in HD and an increasing dimensionality with increasing HD severity. Microstate analysis revealed parameter increases for classes A and B (coverage), decreases for C (occurrence) and D (coverage and occurrence). Disease severity and poorer test performances correlated with parameter increases for class A (coverage and occurrence), decreases for C (coverage and duration) and a dimensionality increase.
Conclusions: Global state changes may reflect higher functional dissociation between brain areas and the complex microstate changes possibly the widespread neuronal death and corresponding functional deficits in brain regions associated with HD symptomatology.
Significance: Combining global- and microstate analyses can be useful for a better understanding of progressive brain deterioration in HD.

1. Introduction

Huntington's disease (HD) is an autosomal-dominant trinucleotide repeat disorder leading to severe neurologic, psychiatric, and cognitive symptoms. Its core pathology is caused by a pathologic elongated gene, which results from a base triplet elongation (CAG) on chromosome 4. This gene produces a protein called Huntingtin, which leads to neural apoptosis especially in the striatum. Typically, first symptoms of HD appear between the ages of 30–50. Following disease onset, patients usually have a remaining life expectancy of 10–15 years (Roos, 2010, Walker, 2007). Deterioration of executive functions, short-term memory and visuo-spatial functioning are followed by the onset of subcortical dementia in later disease stages (Kirkwood et al., 2000).

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Disease conditions can be regarded as gross altered states within which shorter altered or aberrant states are embedded (Lehmann et al., 1987). Electroencephalography (EEG) is an appropriate method for the investigation of global states and due to its very high time resolution it is also perfectly suited for the study of the briefer states (microstates) embedded therein. EEG frequency spectra and source localization analyses have been used in previous HD research (for a review, see Piano et al., 2017). The most consistent findings were a decreased alpha and increased delta and theta frequency band activity. In order to better understand the brain electric changes associated with the complex symptomatology of HD, the present study compared a group of un-medicated HD patients to a group of healthy controls using EEG measures of both global states and microstates.

Global states can be described using measures of dimensional complexity. These are indicators of the number of independent brain processes active in the brain (Wackermann et al., 1993) and have for example been applied to describe gross states such as sleep stages (Szelenberger et al., 1996b). Global states differ between normal healthy controls and depressed (Szelenberger et al., 1996a) and schizophrenic patients (Saito et al., 1998) and have been proposed as measures of brain maturation (Stam et al., 2000). In the present study, we chose omega complexity (Wackermann, 1996) as a first measure to describe the global state of HD patients. Informally, omega complexity takes the eigenvalues of the covariance of brain activity measures from/with scalp EEG or cortical activity signals and calculates the number of independent sources. The detailed calculation procedure and the justification for its interpretation can be found in (Wackermann, 1996, Wackermann and Allefeld, 2009). Omega complexity has been studied in other disease conditions. It was increased in schizophrenic (Irisawa et al., 2006, Saito et al., 1998) and Alzheimer patients (Czigler et al., 2008, Yoshimura et al., 2004) compared to healthy controls.

We selected a connectivity measure, global lagged connectivity, as a second measure to describe the global state of HD. While complexity measures approximate the number of functionally independent system units, connectivity measures assess the cooperativity between system units. Thus, both measures are indicators for dissociation between brain areas. Connectivity measured as coherence was reported to be increased as well as decreased in schizophrenic patients, with a tendency for decreased coherence in medication-naive, younger, first episode patients (see Lehmann et al., 2014). Coherence was reduced in patients with Alzheimer's disease (e.g. Wang et al., 2014) and in disorders related to depression (Varlamov and Strelets, 2012).

To study the finer-grained aberrations or processing steps embedded in the underlying global state, a microstate analysis was performed. The EEG can be looked at as electric potential distributions on the head surface ('scalp maps') at each moment in time. The EEG microstate analysis searches for scalp maps that show quasi-stable electric potential distributions over prolonged periods of time, called 'microstates' (Lehmann et al., 1987, Lehmann et al., 1998). In using the EEG's very high time resolution, the microstate analysis reveals microstate durations typically in the range of 60–120 milliseconds.

Different scalp potential distributions must have been generated by different spatial distributions of neuronal electric activity in the brain. Therefore, it is reasonable to assume that different microstates embody different types of information processing. EEG microstates have been referred to as putative 'atoms of thought and emotion' (Lehmann, 1990, 2013). Several classes of microstates have been identified (e.g. Koenig et al., 2002, Michel and Koenig, 2018). In spontaneous resting state EEG, typically four classes of microstates are found (Michel and Murray, 2012) that are usually labelled A, B, C, and D.

The microstates of the different classes can be described using parameters such as their number of occurrences, how much time they cover and their mean duration (see methods Section 2.3.3 below). These parameters typically differ between different states and task conditions. Alterations of the microstate parameters have been reported for different microstate classes in normal states of consciousness (non-REM sleep - all classes: Brodbeck et al., 2012, modalities of thinking- all classes: Milz et al., 2016, personality characteristics - classes B and C: Schlegel et al., 2012) (self-related/unrelated thoughts, mental arithmetic - classes B, C and D: Bréchet et al., 2019), altered states of consciousness such as meditation (class B: Faber et al., 2005) (all classes: Zanesco et al., 2019) and hypnosis (classes A, C, and D: Katayama et al., 2007), but also disorders like schizophrenia (all classes: Andreou et al., 2014, Irisawa et al., 2006, Kindler et al., 2011, Koenig et al., 1999, Lehmann et al., 2005, Strelets et al., 2003), euthymic bipolar disorder (class A: Damborská et al., 2019) and fronto-parietal dementia (class C: Nishida et al., 2013). See also Khanna et al. (2015) for a review. Accordingly, the microstate analysis seems especially promising for detecting differences in attention-related, mentation-related and reality-testing related processing.

In addition to the measures of brain-electric activity, cognitive and behavioural symptoms as well as performance of HD patients were probed with the Unified Huntington's Disease Rating Scale (UHDRS, Huntington study group, 1996) and proven cognitive tests.

Based on the findings briefly reviewed above we deducted the following hypotheses:

I) HD patients display significantly altered global characteristics (increased omega complexity and decreased global lagged connectivity) in comparison to healthy controls.
II) HD patients show significant aberrations of all four microstate classes (A, B, C, D) when compared to healthy controls.
III) Aberrations of microstate classes correlate significantly with disease severity and the decline of cognitive and behavioral performance.

2. Methods

2.1. Participants

EEG data of 20 un-medicated HD patients with the genetic diagnosis of HD and of 20 healthy, age, and gender matched controls were available for the present study. The investigation was carried out in accordance with the ethical standards put forth in the Helsinki Declaration. The Ethics Committee of the Medical University of Graz, Austria approved this study (Project No. 31-317ex18/19).

The patient group consisted of 11 males and 9 females (mean age: 41.37 years, SD = 9.15 years). All patients fulfilled the criteria for the International Classification of Diseases, Tenth Revision (ICD-10, World Health Organization, 1993) diagnoses G 10 and F 02.2. The control group consisted of 20 drug-free (age- and sex-matched) healthy controls (11 males, 9 females; mean age: 41.00 years, SD = 11.64 years), that had been recruited by advertisements. Controls displayed no physical, neurological or mental illness. Control data had been stored in a data pool.

HD stages (severity) were graded according to Shoulson's clinical stages (Shoulson and Fahn, 1979). At stage 1, patients clinically show minimal impairment and function at their usual level; at stage 5 patients are severely affected, suffer from pronounced motor and cognitive impairment and require institutional care. Twelve of our patients were in stage 1, 3 patients in stage 2 and 5 patients in stage 3.

2.1.1. Behavioral data

Apart from the gradation into clinical HD stages mentioned above, additional behavioral and cognitive variables were assessed via questionnaires. The UHDRS was used as customary in many HD centers (Paulsen, 2011). The motor section of the UHDRS (Huntington Study Group, 1996) was applied to probe for motor function disturbances. The Stroop Interference Test (Stroop, 1935, 1992) with color, word and interference subtests, and the Verbal Fluency test (VF, Benton et al., 1994) were served to screen executive functions. The Stroop test measures conflict resolution and inhibition of prepotent responses, and the VF test assesses internally guided word search and production necessitating the suppression of retrieval/production of inappropriate words and output monitoring. German versions of the Stroop and VF tests were used. The Symbol Digit Modality Test (SDMT, Smith, 1968, 1982) was used to assess information processing (attention, perceptual speed, motor speed and visual scanning) and the Mini–Mental State Examination (MMSE, Folstein et al., 1975) to screen for signs of dementia.

2.2. Data recording

The recordings of all participants consisted of a nineteen-channel EEG. The electrode placement was based on the international 10–20-system: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2. All electrodes were referenced against averaged mastoids. The data were recorded with a Nihon Kohden 4421 G polygraph. Participants had been kept alert by the technician with a tapping sound whenever drowsiness patterns appeared in the record.

2.3. Data analysis

2.3.1. Data preprocessing

From the vigilance controlled task-free resting EEG data, artifact-free epochs were selected after minimizing ocular artifacts by regression analysis in the time domain using an automatic artifact identification method (Anderer et al., 1992) and after subsequent visual inspection for remaining artifacts.

The following preprocessing steps were applied to the data in view of the microstate analysis and their compatibility with the global state analysis. The available 19-channel artifact-free EEG data were segmented into 2-s epochs. For the patient group, there was an average of 28.7 artifact-free 2-second epochs available (SD = 16.2; range: 8–62) per patient. For the control group, 12 artifact-free 2-second epochs were available per participant from the data pool, for which only the first 12 artifact-free epochs had been selected. The available data were then re-referenced to the average reference and FFT-filtered between 2–20 Hz, as commonly applied for microstate analyses (see Michel and Koenig, 2018). In order to stay compatible with the microstate analysis, the global state analyses were performed with the same broad band.

2.3.2. Global state analysis

The global or background states in HD patients and normal, healthy controls were assessed using a dimensionality and a connectivity measure.

Rather than computing dimensionality and connectivity on scalp-recorded potential differences (Chella et al., 2017, Lehmann et al., 2006, Marzetti et al., 2007), these measures were estimated from intracortical signals using exact low resolution electromagnetic tomography (eLORETA; Pascual-Marqui, 2007a). eLORETA uses a solution space of 6239 voxels. In order to obtain an estimate for the global dimensionality and connectivity, 19 regions of interest (ROIs) were used. Each ROI was defined by the single underlying cortical grey matter voxel closest to each of the 19 electrode positions of the 10–20 system. Using one voxel for the definition of the ROIs is adequate due to the smoothness constraint of the LORETA solution. The following global measures are based on these 19 eLORETA ROI signals, band-pass filtered from 2-20 Hz, computed for each participant in each group.

Both omega complexity and global lagged connectivity were computed using an implementation of the respective algorithms (lagged connectivity: Pascual-Marqui, 2007b, Pascual-Marqui et al., 2011) (omega complexity: Wackermann, 1996, 1999, Wackermann and Allefeld, 2009) in the eLORETA software package (version 2020–04-14, freely available at https://www.uzh.ch/keyinst/loreta.htm).

Omega complexity (Wackermann, 1996, 1999, Wackermann et al., 1993) is a single-value measure that assesses the dimensional complexity of multi-channel signals. In effect, it is a global measure that gives an approximation to the number of independently active processes in the brain. In the present study, omega complexity computations are based on the complex valued covariances between signals in the frequency domain, more specifically, on the Hermitian cross-spectral matrices, as performed, e.g. in Molnár et al. (2006). Thus, this generalization takes into account phase information, i.e. both instantaneous and lagged dependencies between brain processes.

As previously mentioned, connectivity computations in this study are based on the estimated cortical source signals. However, these signals are affected by volume conduction and low spatial resolution, which are known to produce unduly high coherence values with zero-lag. This means that the estimated cortical signals consist of an instantaneous mixture of the actual signals. One early remedy for this problem was proposed by (Nolte et al., 2004), which retains only the imaginary part of the coherence. In this present study, a related but different measure is used, namely the "lagged coherence", which has been demonstrated to be invariant to the instantaneous mixture of signals (Pascual-Marqui et al., 2018). The "global lagged coherence" defined in (Pascual-Marqui, 2007b) is intended as a single-value measure for the global connectivity (lagged connectivity) characterizing the underlying global state of HD patients and controls.

2.3.3. Microstate analysis

The EEG microstate analysis methodology has recently been reviewed by Michel and Koenig (2018). Following the classical procedure for microstate computation, in a first step the global field power (GFP, Lehmann and Skrandies, 1980) curve was computed in each 2-s epoch. All potential maps at times of maximal GFP ('GFP-peaks') were selected across all epochs per participant. The GFP-peak maps represent potential maps at times of optimal signal-to-noise ratio and around GFP-peaks map topographies remain stable while they change in GFP-troughs (Koenig et al., 2002). Therefore, in a second step only these GFP-peak maps were then fed into a modified k-means clustering algorithm (Pascual-Marqui et al., 1995) that uses Global Map Dissimilarity (Lehmann and Skrandies, 1980) as clustering criterion and that produced for each participant 4 individual model maps ('microstate classes') that best explained the variance in the data. The use of a cross validation criterion has previously shown that 4 model maps constitute an optimal solution (Koenig et al., 1999). In a third step, the individual model maps of all the participants of each group (patients and controls) were used to compute mean group model maps using a permutation algorithm that maximizes the common variance over participants (Koenig et al., 1999). The two sets of four group model maps (patients and controls) were then used to compute a set of 4 grand mean model maps (classes) using the same procedure. In order to remain comparable to previous publications, these grand mean classes were then related in a fourth step to the

4 normative microstate classes published by Koenig et al. (2002) and were labeled accordingly as microstate classes A, B, C and D.

In a final step, all GFP peak maps were attributed to one of the four grand mean classes. A 'microstate' is defined by consecutive GFP-peak maps of the same class. The start of each microstate is defined by the midpoint between the last GFP-peak map of the preceding microstate and the first GFP-peak map of the current microstate, and analogous for the end of each microstate. Since the start of the first microstate and the end of the last microstate of each 2-s epoch is unknown, the first and the last microstates were omitted for the computation of the typical microstate parameters: occurrence, coverage over time and duration. The 'occurrence' is the mean number of occurrences of a certain class per second across all epochs. The 'coverage' is the mean percentage of time covered by a certain microstate class across all occurrences of that class per second across all epochs. The 'duration' is the mean duration of a certain microstate class of all its occurrences per second across all epochs.

The microstate analysis was computed using keypy, an open source python script library developed at the KEY Institute for Brain-Mind research, Zurich (Milz, 2016, Milz et al., 2016), which is freely available from: https://github.com/keyinst/keypy.

2.3.4. Correlation analyses

In the patient group, Pearson correlations were computed between the behavioral and cognitive data (i.e. the stage of the disease, the scores on the MMSE, the motor UHDRS, the SDMT, the Stroop tests and the VF test) and the connectivity and complexity measures as well as the microstate parameters. Further, the microstate parameters and the connectivity and complexity measures were correlated. The significance threshold was at uncorrected $p < 0.05$ and the effect sizes for the correlation coefficients (medium: >0.3, large: >0.5; see e.g. Cohen, 1988, Poldrack et al., 2008) are also reported.

2.3.5. Statistical analyses

A manova was computed for each microstate parameter (coverage, occurrence and duration) to compare groups (HD patients and matched controls) using microstate class as repeated measure. Post-hoc unpaired t-tests for unequal variance were used to untangle significant interaction (class × group) effects, i.e. between groups per class.

A one-way anova was computed to compare groups (HD patients and matched controls) for global lagged connectivity and omega complexity as dependent variables. Post-hoc unpaired t-tests for unequal variance were used to untangle main effects.

3. Results

3.1. Behavioral data

Our HD patient group consisted of mild to moderate stage patients (Shoulson's clinical stages 1–3; Shoulson and Fahn, 1979). All patients were symptomatic and revealed impairments in one or more of the cognitive and behavioral tests. The mean scores and standard deviations were as follows: UHDRS motor section: 22.05 (19.50); MMSE: 21.25 (5.08); Stroop color: 53.75 (22.07); Stroop word: 59.35 (25.94); Stroop interference: 26.65 (10.79); VF test: 22.85 (10.10); SDMT: 24.85 (13.44). Lower test scores generally indicate impairment, except for the UHDRS motor score where a higher score means higher impairment.

3.2. Global state analyses

Global state measures showed a significant main effect in the anova group comparisons (Table 1a). Post-hoc t-tests showed that only global lagged connectivity differed between controls and HD patients, while omega complexity did not. Patients showed a significantly lower (0.42 (0.23)) global lagged connectivity than controls (0.70 (0.37), $p = 0.007$) (Table 1b).

Correlations with the stage of the disease within patients showed no correlation for global lagged connectivity, but a positive correlation at uncorrected $p < 0.05$ for omega complexity ($r = 0.45$) with a medium effect size (>0.3), omega complexity thus increasing with the severity of the disease.

3.3. Microstate analysis

The four grand mean microstate classes (Fig. 1) extracted from the EEG were very similar to the 4 classes from the normative database (Koenig et al., 2002).

The manovas did not show any significant group effects for the microstate parameters independent of class, but revealed significant interaction-effects of class * group for both coverage and occurrence ($p < 0.05$) and a trend for duration ($p = 0.087$; Table 2a). The post-hoc unpaired t-tests for the microstate parameters revealed those classes for which the parameters significantly differed between the two groups (Table 2b). In HD patients compared to their matched healthy controls, microstates of classes A and B had higher coverage ($p < 0.05$) and a trend of higher duration ($p < 0.10$). Microstate class C had lower occurrence ($p < 0.05$) and a trend of lower coverage ($p < 0.10$). Microstate class D had lower coverage and occurrence ($p < 0.05$). Table 3 illustrates the directional changes of the microstate parameters from controls to HD patients for all comparisons.

3.3.1. Correlations between global state and microstate measures and the behavioral and cognitive data

Table 4 depicts the results of the correlation analyses between the behavioral data and global state measures with the microstate parameters (Table 4a) and the behavioral data with the global state measures (Table 4b). Scatterplots of all significant correlations are illustrated in Supplementary Figures S1–S3.

There were no significant correlations between global lagged connectivity and any of the behavioral or cognitive scores. Omega complexity on the other hand showed a significant positive correlation with the stage of the disease and significant negative correlations with the MMSE, the Stroop interference and the VF tests.

The behavioral and cognitive scores revealed some significant correlations with the microstate parameters. The stage of the disease (severity) was positively correlated with microstate class A coverage and occurrence as well as negatively correlated with microstate class C coverage and duration.

The motor UHDRS scores showed merely a significant positive correlation with class A coverage.

The MMSE scores were not correlated with the microstate parameters.

Both the scores on the Stroop tests and the SDMT were negatively correlated with class A occurrence (and coverage for the Stroop word test) and positively correlated with class C coverage (except for Stroop interference) and duration.

The VF test scores were not correlated with the microstate parameters.

The behavioral and cognitive scores all correlated significantly with the stage of the disease (Table 5), indicating a worsening in the tests with increasing HD severity.

Table 1a
Results of one-way anova group comparison (Huntington's Disease patients versus controls) for global state measures (global lagged connectivity and omega complexity) as dependent variables.

	Wilks' Lambda	df	F	p-value
group	0.813	2.0, 37.0	598.724717	**0.022**

Significant p-values at $p < 0.05$ are bolded.

Table 1b
Global state group comparisons: means, standard deviations and p-values for unpaired post-hoc t-tests.

	Global lagged connectivity	Omega complexity
	mean (sd)	mean (sd)
HD patients	0.42 (0.23)	4.72 (0.90)
controls	0.70 (0.37)	4.47 (0.92)
p-value	**0.007**	0.381

HD: Huntington's Disease; significant p-values at $p < 0.05$ are bolded.

3.3.2. Correlations between microstate and global state measures

The two right columns of Table 4a list all correlations between global and microstate measures in the patient group.

Global lagged connectivity was negatively correlated with microstate class A occurrence and positively correlated with microstate class C duration.

Omega complexity did not show any significant correlations with the microstate parameters.

4. Discussion

Considering the progressive widespread neuronal death and the complex symptomatology consisting of motor, cognitive and psychiatric symptoms of HD, we expected wide-ranging differences of global- and microstate EEG measures in un-medicated HD patients compared to healthy age and gender matched controls. As expected, we observed extensive changes in all EEG measures in HD patients. In the patient group, we additionally found correlation patterns between cognitive and behavioral data and EEG measures.

4.1. Global state results

The two global state measures showed interesting results. On the one hand, global lagged connectivity was lower in patients than controls, while omega complexity did not differ. On the other hand, omega complexity showed a positive correlation with the stage of the disease while global lagged connectivity did not. Omega complexity approximates the number of functionally independent system units while global lagged connectivity is a measure of the interaction between system units. HD thus seems characterized by underlying global states showing an increasing number of independent processes with increasing severity of the disease and significantly less cooperation between brain areas independent of the severity of the disease, indicating an increased dissociation in HD.

While all correlations between omega complexity and the behavioral and cognitive test scores revealed at least medium ($r > 0.3$) effect sizes, only those for the MMSE, the Stroop interference test and the VF test reached significance. As all behavioral and cognitive tests correlated significantly with HD stage showing that the test performance worsened with the progression of the disease, these results indicate that the worsening of the test performance was associated with increasing dimensionality, i.e. increased dissociation.

4.2. Microstate results

As expected, the EEG microstate analysis revealed changes of the parameters of all 4 microstate classes in patients suffering from HD compared to healthy, age and gender matched controls. These results suggest that the symptomatology of HD is reflected in abnormal steps of information processing. The main findings were an increase in one or more parameters for microstate classes A and B and a decrease for classes C and D. The fact that all four microstate classes are affected by HD may reflect the complex symptomatology and neuronal deterioration of this disease.

The functional significance of the four microstate classes and of their interplay is not yet fully established but has lately been the target of several studies (Britz et al., 2010, Custo et al., 2017, Milz et al., 2016, Pipinis et al., 2016, Seitzman et al., 2017). In the following paragraphs, our results are discussed in the light of what is known about the functional significance of the different microstates classes.

4.2.1. Alterations of microstate classes a and B

In HD patients, we observed a significantly increased coverage and a trend towards an increased duration of both classes A and B.

Increased coverage of class A microstates was reported in individuals at high risk of psychosis (Andreou et al., 2014) and in patients with panic disorder (Kikuchi et al., 2011). It has been proposed that an increase in class A prominence could be a predictor of psychotic transition or an unspecific indicator of anxiety (Andreou et al., 2014). With increasing severity of HD, both psychotic symptoms (e.g. delusions) and anxiety symptoms (e.g. paranoia) emerge (Kirkwood et al., 2001). Thus, our results seem in line with one or both of these observations.

Class A coverage and occurrence were increased in patients with Parkinson's disease (PD) and correlations linked class A occurrence to motor function (Chu et al., 2020). These results only partly match our own. We also found a trend towards increased class A coverage, but we found no difference in occurrence compared to

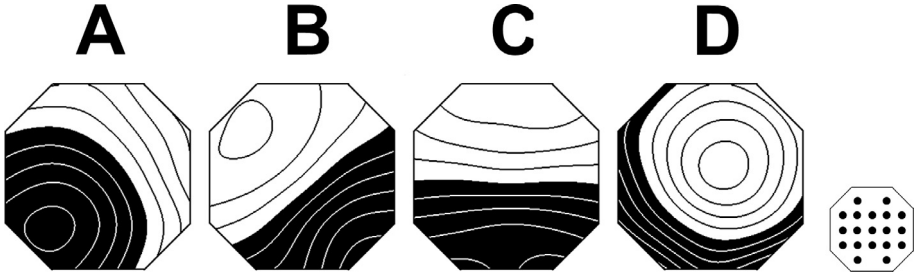

Fig. 1. The grand mean model maps of the four microstate classes. Equipotential area maps are shown. Semi-schematic electrode array in inset. Head seen from above, nose up, left ear left. The isopotential contour maps show the (arbitrarily assigned) areas of opposite polarity in black and white (normalized voltage values). A-D: microstate class labels.

Table 2a
Results of manova group comparisons (Huntington's Disease patients versus controls) for each microstate parameter (coverage, occurrence and duration) with microstate classes (A, B, C and D) as repeated measure.

	Wilks' Lambda	df	F	p-value
coverage				
class	0.362	3.0, 36.0	21.128	**0.000**
class * group	0.645	3.0, 36.0	6.604	**0.001**
occurrence				
class	0.381	3.0, 36.0	19.500	**0.000**
class * group	0.638	3.0, 36.0	6.814	**0.001**
duration				
class	0.421	3.0, 36.0	16.496	**0.000**
class * group	0.835	3.0, 36.0	2.368	0.087

Significant p-values at $p < 0.05$ are bolded; trends at $p < 0.10$ are underlined.

Table 2b
Microstate parameters per microstate class: means, standard deviations and p-values of unpaired post-hoc t-tests.

	class A mean (sd)	class B mean (sd)	class C mean (sd)	class D mean (sd)
coverage				
controls	19.30 (5.94)	22.98 (4.09)	34.65 (5.37)	23.07 (6.39)
HD patients	23.53 (6.34)	28.13 (5.48)	30.29 (8.30)	18.09 (4.24)
p-value	**0.036**	**0.002**	0.057	**0.007**
occurrence				
controls	3.06 (0.98)	3.44 (0.58)	4.36 (0.60)	3.48 (0.54)
HD patients	3.34 (0.79)	3.76 (0.69)	3.78 (0.74)	2.85 (0.67)
p-value	0.320	0.122	**0.009**	**0.003**
duration				
controls	63.75 (10.53)	67.75 (13.38)	80.31 (14.13)	66.28 (14.43)
HD patients	70.60 (13.53)	75.44 (12.34)	80.27 (15.67)	64.30 (9.63)
p-value	0.082	0.066	0.994	0.612

HD: Huntington's Disease; significant p-values at $p < 0.05$ are bolded; trends at $p < 0.10$ are underlined.

Table 3
Directional changes of microstate parameters between groups per microstate class.

	from controls to un-medicated HD patients			
	A	B	C	D
coverage	↗	↗	↘	↘
occurrence	-	-	↘	↘
duration	↗	↗	-	-

A-D: microstate class labels; HD: Huntington's Disease; bold and larger arrows: $p < 0.05$; standard arrows: $p < 0.10$ (trend); - no change.

controls in our HD patients. Also, while Chu et al. (2020) reported decreasing occurrence with increasing deterioration of motor function, we found increasing coverage with increasing deterioration of motor function. These results suggest a relation of class A to motor function, but they also seem to imply differences between HD and PD patients.

Microstate class A coverage increases were linked to apathy in schizophrenic patients (Giordano et al., 2018). More precisely, avolition apathy correlated positively with class A coverage and the authors suggested that the motivational deficits might be related to underlying sensory processing abnormalities (Giordano et al., 2018). Apathy is considered a very common feature of HD (Camacho et al., 2018). The precise characteristics of apathy in HD are not yet clearly defined, validated assessment tools in HD are still missing and studies are scarce (Camacho et al., 2018). While the link of increased class A coverage to apathy is interesting, it remains hypothetical in the present dataset, as apathy was not assessed in our patients.

Class B alterations have been reported in different normal, altered and diseased states of consciousness. Class B decreases in all parameters were reported in light hypnosis (Katayama et al., 2007), the duration was decreased in schizophrenic patients (Lehmann et al., 2005, Nishida et al., 2013), the coverage was increased in schizophrenic patients (Andreou et al., 2014), occurrence and coverage were increased in believers in paranormal phenomena as compared to skeptics (Schlegel et al., 2012) and duration was increased in very experienced meditators during deep meditation (Faber et al., 2005). While these findings are too inconsistent to draw any conclusions, a very recent study (Chu et al., 2020) reported results that seem more promising for the interpretation of the present findings. They found increased class B coverage in patients with PD and that increased class B duration correlated with cognitive performance. We also found increased class B coverage and a trend towards increased duration, which could thus be related to the hampered cognitive performance we see in our HD patients.

Several studies aimed to associate microstate classes A and B with modality-specific, visual or verbal / phonological processing (Britz et al., 2010, Custo et al., 2017, Milz et al., 2016, Seitzman et al., 2017). Recent results suggest that class A prominence was increased when alpha inhibition was increased over left posterior language related areas, and class B prominence was increased

Table 4
Pearson Product Moment correlations between microstate and global state measures and behavioral data for the Huntington's Disease patient group (N = 20).

	HD stage	MMSE	UHDRS (motor)	Stroop (word)	Stroop (color)	Stroop (interf.)	Symb. Digit	Verbal Fluency	Glob. lag. connect.	Omega complexity
a) Coverage										
class A	**0.49**	−0.29	**0.46**	**−0.53**	−0.42	−0.33	−0.42	−0.35	−0.32	0.33
class B	0.14	0.21	−0.01	0.03	−0.36	−0.05	−0.23	0.21	−0.11	−0.20
class C	**−0.57**	0.21	−0.37	**0.53**	**0.62**	0.41	**0.56**	0.18	0.43	−0.12
class D	0.19	−0.25	0.06	−0.29	−0.11	−0.25	−0.18	−0.09	−0.21	0.01
Occurrence										
class A	**0.51**	−0.28	0.36	**−0.49**	**−0.55**	**−0.44**	**−0.47**	−0.38	**−0.57**	0.27
class B	0.22	0.08	−0.02	0.01	−0.40	−0.23	−0.25	0.01	−0.33	−0.01
class C	−0.32	0.07	−0.21	0.30	0.21	0.05	0.20	0.07	0.07	0.01
class D	0.23	−0.30	0.06	−0.29	−0.23	−0.36	−0.27	−0.22	−0.25	0.07
Duration										
class A	0.11	−0.02	0.23	−0.16	0.04	0.09	−0.03	0.02	0.14	0.07
class B	−0.04	0.19	0.05	0.04	−0.01	0.20	−0.02	0.25	0.24	−0.22
class C	**−0.51**	0.28	−0.32	**0.48**	**0.69**	**0.58**	**0.62**	0.25	**0.53**	−0.21
class D	−0.09	0.17	−0.02	0.07	0.24	0.28	0.18	0.28	0.11	−0.17
b) Glob. lag. connectivity	−0.17	0.17	−0.14	0.29	0.36	0.36	0.28	0.26		
Omega complexity	**0.45**	**−0.46**	0.39	−0.38	−0.43	**−0.55**	−0.43	**−0.59**		

HD: Huntington's Disease, MMSE: Mini–Mental State Examination, UHDRS: Unified Huntington's Disease Rating Scale; significant correlation coefficients at uncorrected $p < 0.05$ are bolded; a single underline indicates a medium effect size ($r > 0.3$), a double underline a strong effect size ($r > 0.5$).

Table 5
Pearson Product Moment correlations between behavioral and cognitive scores and Huntington's Disease stage (severity) for the Huntington's Disease patient group (N = 20).

	MMSE	UHDRS (motor)	Stroop (word)	Stroop (color)	Stroop (interf.)	Symb. Digit	Verbal Fluency
HD stage	−0.48	0.64	−0.65	−0.82	−0.70	−0.66	−0.46

HD: Huntington's Disease, MMSE: Mini–Mental State Examination, UHDRS: Unified Huntington's Disease Rating Scale; all correlations were significant at uncorrected $p < 0.05$; a single underline indicates a medium effect size (>0.3), a double underline a large effect size (>0.5).

when alpha inhibition was increased over right posterior visuo-spatial related areas (Milz et al., 2017). Consequently, our observed increase in class A and B microstate prominence in HD might reflect an increased inhibition and thus disturbance of both verbal and visual functioning in HD patients. This would be in line with the worsening of the performance in the cognitive tests seen in HD patients.

4.2.2. Alterations of microstate classes C and D

Class C microstates have been associated with activity in two important hubs of the default mode network (DMN, Raichle et al., 2001): the anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC) (Pascual-Marqui et al., 2014). An earlier study reported class C microstate correlations with positive blood oxygen level dependent (BOLD) signals in the ACC, the bilateral frontal gyri and the right insula (Britz et al., 2010), regions belonging to the resting state network 6 in Mantini et al. (2007). These areas overlap with the saliency network and were linked to subjective interoceptive-autonomic processing. Class C processing thus possibly is involved in the integration of interoceptive information with emotional salience to form a subjective own body representation (Britz et al., 2010).

In the present study, un-medicated HD patients showed reduced occurrence and a trend for reduced coverage of class C microstates. Also, the coverage and duration correlated negatively with the stage of the disease. This is in line with results showing that cell loss in the ACC correlates with HD symptomatology during the course of the disease (Thu et al., 2010). Considering these findings, one might speculate that in HD patients the progressive motor decline and failing emotional salience attribution is partly related to an impaired class C processing. This could be due to the increasing attention demanding aspects of the coordination and involuntary movement related symptoms of the disease when it progresses to advanced stages or due to cell loss during the course of the disease. Interestingly, during light hypnosis, class C microstates also show decreased prominence, possibly due to the increased inward-directed attention to bodily perceptions (Katayama et al., 2007). This is in line with Pipinis et al. (2016) who reported a negative correlation of class C microstate coverage with experienced somatic awareness.

Class D microstates in HD patients were characterized by a general reduction of coverage and occurrence compared to controls. Reduced microstate parameters have been reported in several studies. Schizophrenia studies reported reductions in one (Kindler et al., 2011, Nishida et al., 2013), two (Kikuchi et al., 2007) or all three (Tomescu et al., 2014) class D microstate parameters. A meta-analysis (Rieger et al., 2016) confirmed both a shortened class D duration and a reduced class D coverage in schizophrenia. During deep hypnosis class D duration was shortened and coverage reduced (Katayama et al., 2007). During non-REM sleep, class D duration was prolonged but its occurrence was reduced (Brodbeck et al., 2012). Together these studies suggest that all three microstate parameters can be affected in reality remote states, most often reflected in a reduction of the corresponding parameters. Based on these findings, it has been suggested that class D microstates reflect processes involved in reality testing (Milz et al., 2016, Rieger et al., 2016). The actual contribution or involvement of each parameter or the details of their interplay regarding their role in reality testing are still unclear. Nevertheless, the literature suggests that some or all microstate class D parameters are modulated by reality testing processes. The reduced prominence of class D microstates in HD patients could thus indicate a reduced activation of processes associated with reality testing.

As mentioned above, Milz et al. (2017) reported that the frequency band-wise source localization differences between the microstate classes are predominantly defined by the alpha activity; also, classes C and D both showed highest underlying alpha activity. Most EEG studies reviewed by Piano et al. (2017) reported a decrease in alpha activity in HD, which appears to be a trait marker of HD (Painold et al., 2010, 2011). Our reported decrease in class C and D prominence is thus in line with these observations.

4.2.3. Microstate interactions

In general, it is plausible to assume that the interplay between the microstate classes is crucial for the constitution of different normal, abnormal and diseased states of consciousness. In a microstate study on hypnosis (Katayama et al., 2007), light hypnosis only showed a decreased occurrence and coverage of class C compared to resting while in deep hypnosis occurrence and coverage of class A was increased and duration and coverage of class D decreased. HD patients also showed an increase of class A coverage, a decrease of class C occurrence and a decrease of class D coverage and occurrence. HD thus shares some characteristics of both light and deep hypnotic conditions. Hypnosis has been characterized as focused attention, enhanced somatic and emotional control, and lack of self-consciousness (Jiang et al., 2016). It has also been argued that hypnosis is characterized by a functional dissociation of conflict monitoring and cognitive control processes (Egner et al., 2005). As mentioned before, ACC-cell loss correlated with HD symptomatology (Thu et al., 2010) and in a functional neuroimaging study the ACC was less recruited in individuals highly susceptible to hypnosis (Cojan et al., 2015), which could account for HD patients reflecting similar microstate patterns as people in hypnotic states.

Cognitive decline in patients with Alzheimer's disease correlated positively with a general microstate duration decrease (Strik et al., 1997). In contrast, we found a trend towards increased class A and class B durations in our HD patients, which could be due to the fact that they were in initial to moderate disease stages. Cognitive decline has been linked to class C occurrence decreases and class B duration increases in PD patients (Chu et al., 2020), which seems in line with our results showing decreased class C occurrence and a trend towards increased class B duration in HD patients, thus possibly reflecting the cognitive decline seen in HD patients. In schizophrenia, class C occurrence increased and class D duration decreased (Rieger et al., 2016), whereas in our initial to moderate HD patients we observed decreases in class C occurrence and class D coverage and occurrence. Psychotic symptoms predominantly occur in late stages of HD - it is not known however whether late stage HD patients would show a pattern similar to patients with schizophrenia. Also, the four microstate classes are typically alternating and the microstate syntax – i.e. the concatenation of microstates of different classes – is known to differ in different normal and pathological states (Lehmann et al., 2005, Schlegel et al., 2012). Therefore, the interplay of the microstate classes might be related to behavioral effects and clinical symptoms in HD patients.

The general pattern of our results is very similar to that of PD patients reported by Chu et al. (2020). PD patients also showed microstate parameter increases for classes A and B and decreases for classes C and D. These similarities might be due to cognitive and motor function declines seen in both diseases, while the differences in which parameters were significantly affected might be due to the underlying physiological differences between HD and PD.

4.3. Correlation results

When studying all correlation results as listed in Table 4, a clear pattern emerges: the highest correlations and the largest number of significant correlations (at uncorrected $p < 0.05$ and with medium or large effect sizes) concern microstate class A coverage and occurrence as well as class C coverage and duration. While the group comparisons showed that all classes of microstates are affected by the disease, the correlation results revealed that only classes A and C are related to the progression of the disease. In general, the higher class A prominence and the lower class C prominence, the more advanced the HD symptoms (stage) were and the worse the performance in the cognitive tests, and also the higher the dissociation (increased dimensionality) became. Performance in the cognitive tests was better (all correlations showed at least medium effect sizes, 3 were significant), the lower the omega complexity, which seems to imply increased focused attention for better performance. Considering that class C prominence decreased in HD patients suggesting increased attention and somatic awareness, combined with a class D decrease suggesting reduced reality testing, one might speculate that the focused attention needed for good test performance was disturbed by an increased focus on bodily perceptions and reduced reality testing.

The correlations of class C coverage and occurrence as well as class A occurrence with SDMT scores fit well into this scheme. SDMT scores have been shown to correlate with brain areas related to motor processing, cognitive control, auditory and semantic processing as well as visual processing in a structural magnetic resonance imaging study in prodromal HD subjects (Harrington et al., 2014). This is in line with the function of class C related to saliency (Britz et al., 2010) and of class A modulating language-related areas (Britz et al., 2010, Milz et al., 2016) and possibly motor function (Chu et al., 2020). The SDMT evaluates information processing (attention, perceptual speed, motor speed and visual scanning) and our results thus show that hampered information processing in HD is related to an occurrence decrease of class A microstates as well as a coverage and duration increase of class C microstates.

The ACC and the dorsolateral prefrontal cortex (DLPFC) are mainly implicated when performing a Stroop task (e.g. Egner and Hirsch, 2005, Milham et al., 2003). These areas are most likely reflected by microstate class C (see Custo et al., 2017) which shows reduced coverage and duration with decreasing Stroop task performance in our data. Class A shows increased occurrence and coverage with decreasing Stroop task performance in our HD patients. These results seem to imply disturbed class A and C processing in HD patients during the solving of the Stroop tasks while classes B and D are not affected. Hampered memory and executive functions as well as response selection and attention resource allocation (as measured by the Stroop tasks) are possibly implemented by hampered functioning of the saliency network (class C, Britz et al., 2010) and possibly motor preparation mechanisms (class A, Chu et al., 2020).

We note that while the test scores of verbal fluency showed basically the same correlational pattern with the microstate parameters as the other test scores, none of the correlations reached significance. The reason probably is that speech difficulties typically occur in later stages of the disease (Kirkwood et al., 2001) and indeed, our group of early to moderate stage patients showed on average normal scores. The same can be speculated for the correlations concerning the UHDRS (motor) test, as again, the pattern is the same, but only the correlation with class A coverage reaches significance; the exclusion of advanced stage patients with more severe motor disturbances might have prevented more pronounced correlations. We note though, that all included patients showed above zero scores, thus presenting at least some motor symptoms. We also note that we found a possible relation of class A coverage to motor function, while Chu et al. (2020) reported such a relation with class A occurrence. More studies are needed to unravel the functional significance of the different class A parameters in their possible relation to motor function.

4.4. Limitations

A limitation of the present study is that only medication-free patients were included. Our participant-pool thus only included patients with mild to moderate HD stages. This fact limits generalization of the findings regarding microstate changes during the complete progression of the disease.

Another limitation concerns the rather low number of EEG epochs available in some patients and the therefore possibly low signal to noise ratio, mostly due to the difficulties inherent in recording HD patients showing motor symptoms. Also, there was a significant difference in the number of epochs between patients and controls which stems from the fact that control data was taken from a recruited data pool with a fixed number of epochs available. This discrepancy has been accounted for by using tests for unequal variances.

A further limitation of this study is the small number of electrodes used, namely 19 electrodes of the 10/20 system. The main effect that this has with respect to the eLORETA estimated cortical sources and their dynamics is that there is low spatial resolution, but with exact localization. A number of studies have provided validation for eLORETA with as little as 28 down to 19 electrodes (Dierks et al., 2000, Mulert et al., 2004, Pizzagalli et al., 2004, Zumsteg et al., 2006, Zumsteg et al., 2005).

5. Conclusions

In sum, the present global state results showed that HD is characterized by reduced connectivity and increasing dimensionality (complexity) with disease worsening, suggesting a dissociation between brain regions compared to healthy controls. The microstate results revealed that HD is characterized by alterations affecting all EEG microstate classes with increased prominence of classes A and B and decreased prominence of classes C and D. The correlation analyses disclosed that an excess of class A microstates and a shortage of class C microstates go hand in hand with increasing severity of the disease and worsening of the performance in cognitive tests, and with global state changes indicative of a stronger dissociation of specific brain areas with the progression of disease severity.

Declaration of Competing Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

None of the authors has declared any conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.10.006.

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